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ABNORMAL CORPUS CALLOSUM MYELINATION IN PEDIATRIC BIPOLAR PATIENTS

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Abstract

Background—Decreased signal intensity in the corpus callosum, reported in adult bipolar disorder patients, has been regarded as an indicator of abnormalities in myelination. Here we compared the callosal signal intensity of children and adolescents with bipolar disorder to that of matched healthy subjects, to investigate the hypothesis that callosal myelination is abnormal in pediatric bipolar patients.

Methods—Children and adolescents with DSM-IV bipolar disorder (n=16, mean age ±S.D.= 15.5 ±3.4y) and matched healthy comparison subjects (n=21, mean age ±S.D.= 16.9 ±3.8y) underwent a 1.5 T MRI brain scan. Corpus callosum signal intensity was measured using an Apple Power Mac G4 running NIH Image1.62 software.

Results—Bipolar children and adolescents had significantly lower corpus callosum signal intensity for all callosal sub-regions (genu, anterior body, posterior body, isthmus and splenium) compared to healthy subjects (ANCOVA, all $p<0.05$, age and gender as covariates).

Limitations—Relatively small sample size.

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Conclusions—Abnormalities in corpus callosum, probably due to altered myelination during neurodevelopment, may play a role in the pathophysiology of bipolar disorder among children and adolescents.

Keywords

corpus callosum; magnetic resonance imaging; bipolar disorder; children; adolescents

Introduction

The corpus callosum is the major white-matter fiber tract in the brain and contains most of the axonal transmissions between the two cerebral hemispheres. The corpus callosum supports primary cognitive capacities such as memory, attention, language and intelligence (Giedd et al., 1996). The cortical areas responsible for these capacities develop during childhood and adolescence, as do their extensive network of connections via the corpus callosum. Probably due to ongoing myelination, the corpus callosum increases in size until adulthood (Giedd et al., 1999).

Recently, the signal intensity of the T1-weighted Magnetic resonance imaging (MRI) was used to evaluate the free water content in the brain tissue of subjects with psychiatric disorders to indirectly assess the cytoskeletal architecture. During normal childhood and adolescence, it was demonstrated that the corpus callosum signal intensity (CCSI) decreases due to increase in the free-water (Keshavan et al., 2002).

In adult patients with bipolar disorder, the corpus callosum size is smaller (Coffman et al., 1990, Brambilla et al., 2003) and the CCSI is lower (Brambilla et al., 2004) compared with healthy controls. Corpus callosum size in children and adolescents with bipolar disorder is not abnormal (Yasar et al., 2006). However, the myelination process has not been evaluated.

We examined CCSI, an index of myelination of the corpus callosum, in children and adolescents with bipolar disorder. We hypothesized that, similarly to adults, CCSI would be lower in pediatric bipolar patients compared with healthy subjects, suggesting abnormal callosal myelination as a possible factor in the pathophysiology of early onset bipolar disorder.

Methods

Subjects

Sixteen DSM-IV bipolar disorder patients (BP) (mean age±S.D.= 15.5 ±3.4y, range= 10-21y, 8 females; 12 BP type I, 3 BP II, 1 BP not otherwise specified, 14 euthymic and 2 depressed at scan time) and 21 healthy subjects (mean age±S.D.=16.9 ±3.8y, range= 11-21y, 9 females) were interviewed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1996) or the Structured Clinical Interview for DSM-IV (SCID-IV) (Spitzer et al., 1994). BP patients were co-morbid with: ADHD (n=5), Oppositional Defiant Disorder (n=1) and Conduct Disorder (n=1). Fourteen patients were on mood stabilizers (6 on lithium, 4 on valproate, and 4 on both). Healthy controls were excluded if they, or any of their first-degree relatives, had any DSM-IV axis I disorders. All subjects and their parent or legal guardian gave written informed consent. This study was approved by the University of Pittsburgh IRB.

MRI Procedures

MRI scans were acquired with a 1.5T GE scanner (General Electric Medical Systems, Milwaukee, WI). Three-dimensional-gradient echo imaging (SPGR) was done in the coronal

plane (TR/TE/NEX=25ms/5ms/1, nutation angle=40°, FOV=24cm, matrix size=256×192, slice thickness= 1.5 mm, number of slices= 124).

Corpus Callosum Signal Intensity

Images were analyzed on an Apple Macintosh Power PC (Mac OS7.5.5) using the semi-automated NIH Image software version 1.62. CC was divided into 5 subregions (Witelson, 1989): the genu, anterior body, posterior body, isthmus, and splenium. SI was obtained for each region by measuring a circular area recording the mean pixel intensity. The CC SI was normalized by dividing it by the SI of the vitreous humor, a homogeneous region.

Statistical Analyses

Statistical analyses were conducted in the SYSTAT software, version 8.1 (SPSS, Chicago, IL). The normalized CCSI data were inverse transformed to normalize the distribution. We used analysis of covariance (ANCOVA) with age and gender as covariates to compare the mean CCSI of the 2 groups. We used Pearson's correlations to analyze the association between age and CCSI, and Spearman's correlation to analyze the associations between clinical variables and CCSI. We adopted $p < 0.05$.

Results

BP patients and healthy controls did not differ on age ($t = 1.15$, $df = 35$, $p = 0.26$), gender (*Fisher's exact test*, $p = 0.75$), puberty degree (Mann-Whitney $U = 155.5$, $p = 0.69$) or level of education (Mann-Whitney $U = 128.5$, $p = 0.23$).

All CCSI measurements are displayed in table 1. Pediatric BP had significantly lower CCSI for all subregions compared to healthy controls.

In healthy controls, age was inversely correlated with CCSI at all callosal subregions (genu: $r = -0.56$, $p = 0.009$, anterior body: $r = -0.57$, $p = 0.008$, posterior body: $r = -0.57$, $p = 0.007$ and isthmus: $r = -0.55$, $p = 0.009$; and splenium: $r = -0.54$, $p = 0.011$); whereas bipolar patients did not show any significant correlations ($p > 0.05$).

Because the correlation between CCSI and age (a covariate in the model) differed as a function of diagnostic group, we re-analyzed the data and compared the adjusted means assuming the mean age of the population was 13, 17 and 20 y. This model predicted that at mean ages of 13 or 17 y, bipolar patients would have significantly lower SI in all callosal sub-regions compared with age matched healthy subjects, but at mean age 20 y, the difference would not be significant (table 2).

Male BP ($n = 8$; mean age±S.D.= 14.9 ±4.4y, range= 10-21y) had significantly lower callosal SI in the genu ($F = 4.36$, $df = 1/17$, $p = 0.05$), anterior ($F = 4.44$, $df = 1/17$, $p = 0.05$) and posterior body ($F = 4.48$, $df = 1/17$, $p = 0.05$); and a trend towards lower callosal SI in the isthmus ($F = 3.92$, $df = 1/17$, $p = 0.06$) and splenium ($F = 3.81$, $df = 1/17$, $p = 0.07$) than male healthy controls ($n = 12$; mean age ±S.D.= 16.1 ±3.7y, range= 11-21y). Female BP ($n = 8$; mean age ±S.D.= 16.1 ±2.2y, range= 13-19y) did not show any significant differences from female healthy controls ($n = 9$; mean age ±S.D.= 18 ±3.9y, range= 11-21y). There were no significant differences in CCSI between male and female bipolar patients ($p > 0.05$).

There were no significant correlations between SI of any callosal regions and length of illness (mean±S.D.= 3.9 ±2.4y) or number of episodes (mean±S.D.= 5.1±2.3).

Discussion

Our finding of lower CCSI in adolescents with bipolar disorder compared to healthy controls is consistent with findings in adults with bipolar disorder (Brambilla et al., 2004). Moreover, smaller CC size was found in adult bipolar patients compared to healthy subjects (Coffman et al., 1990, Brambilla et al., 2003), in children and adolescents with Post Traumatic Stress Disorder (De Bellis et al., 1999) and in children who were neglected (Teicher et al., 2004), compared to healthy controls. Nonetheless, in these bipolar adolescents, the CC size was not abnormal (Yasar et al., 2006). The CCSI may be a more sensitive marker of abnormal myelination than the CC size. The SI is sensitive to the tissue properties, most notably the free water content that increases during normal myelination.

By estimating mean adjusted CCSI for subjects at 3 mean ages (13, 17, 20 years), we further evaluated possible abnormal neurodevelopmental processed in the CC. Children and adolescents with BP at ages 13 and 17 years were predicted to have significantly lower CCSI compared with age and sex matched healthy subjects; whereas adults with bipolar disorder (mean age 20 years) would not differ from healthy controls. However, Brambilla et al. (2004) reported lower CCSI in a larger sample of adult BP. Our predictions of lower CCSI in younger BP may indicate that these abnormalities are more pronounced in younger patients.

Keshavan and colleagues (2002) described the decrease in CCSI, which occurs with age in healthy subjects that was replicated by us. The CC is one of the last areas to mature in the central nervous system probably because of its role in the interconnectivity. It presents a rostro to caudal wave of growth until adulthood, and its pruning is dependent on environmental experiences (Giedd et al., 1996; Thompson et al., 2000). During childhood and adolescence, the axonal size increases and the microtubular density decreases. Subsequently the axonal free cytosolic contents increase. This process leads to the increase of the visible water that is detected as lower SI. Interestingly, our pediatric bipolar patients did not show any significant correlations between age and CCSI, which could be interpreted as another evidence of abnormal maturation process.

We observed that male BP had significantly lower CCSI in the genu, anterior and posterior body; whereas female BP did not have any significant difference from female healthy controls. Male healthy controls were recently shown to have lower T1 SI compared to females (Shin et al., 2005). This is in agreement with a *post-mortem* study showing reduced fiber density in male healthy subjects compared to females (Highley et al., 1999). De Bellis et al. (1999) noted that the reduction in CC area was most pronounced in male patients with Post Traumatic Stress Disorder. Taicher et al. (2004) also reported that boys who suffered neglect had significantly stronger effect size for smaller rostral, anterior and posterior body and splenium. However, Hauser et al. (1989) found that male healthy subjects had a significantly greater CC area than female healthy subjects, but they did not report any difference between healthy subjects and affective or schizophrenic patients, nor gender effect on the patient groups. Overall, male children and adolescents suffering from a psychiatric disorder are more vulnerable to CC abnormalities than female individuals.

A limitation of our study could be the psychotropic medication taking by our patients, but possible effect of medication on CC has never been reported. Another limitation is the co-morbid disorders. Nevertheless, the most prevalent co-morbid in our sample, ADHD, seems to increase SI in frontal areas (Pueyo et al., 2003).

Our study provides further evidence for CC abnormalities in the pathophysiology of bipolar disorder. The lower CCSI in pediatric bipolar patients may be due to primary abnormalities in white matter tissue taking place during childhood and adolescence. Alternatively, it could be secondary to a lower demand of brain areas affected by bipolar disorder (Caetano et al.,

2005) that are connected by the CC. The understanding of the CC integrity and its myelination process could progress with the use of the Diffusion Tensor Imaging technique, especially in longitudinal studies.

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Table 1

Signal intensity of corpus callosum in pediatric bipolar patients and healthy controls

Corpus callosum regions	Bipolar Patients n= 16	Healthy Controls n= 21	F	p
Genu	1.29±0.14	1.61±0.56	8.9	0.005
Anterior body	1.28±0.15	1.57±0.51	9.1	0.005
Posterior body	1.28±0.15	1.56±0.50	8.3	0.007
Isthmus	1.27±0.13	1.56±0.53	8.9	0.005
Splenium	1.28±0.14	1.59±0.56	8.9	0.005

Signal intensity measurements are reported as unadjusted mean±S.D.

*ANCOVA with age and gender as covariates all tests have 1/33 df.

Table 2

Estimated mean corpus callosum signal intensity by region of interest and subject age.

Region of Interest	Age	Bipolar	Healthy	F	p
Genu	13	1.42 (1.19, 1.75)	2.04 (1.62, 2.76)	17.5	<**.001**
	17	1.44 (1.20, 1.81)	1.68 (1.39, 2.13)	5.9	**.021**
	20	1.46 (1.18, 1.92)	1.49 (1.23, 1.88)	<1	.841
Anterior Body	13	1.41 (1.19, 1.74)	1.98 (1.59, 2.64)	16.4	<**.001**
	17	1.43 (1.19, 1.76)	1.66 (1.38, 2.08)	6.2	**.018**
	20	1.43 (1.17, 1.86)	1.48 (1.23, 1.85)	<1	.727
Posterior Body	13	1.42 (1.19, 1.75)	1.98 (1.58, 2.64)	15.3	<**.001**
	17	1.43 (1.19, 1.78)	1.65 (1.37, 2.08)	5.5	**.026**
	20	1.44 (1.17, 1.87)	1.47 (1.22, 1.85)	<1	.790
Splenium	13	1.42 (1.19, 1.75)	2.00 (1.59, 2.70)	15.9	<**.001**
	17	1.42 (1.18, 1.77)	1.66 (1.37, 2.10)	6.1	**.019**
	20	1.42 (1.15, 1.86)	1.47 (1.22, 1.85)	<1	.722
Isthmus	13	1.40 (1.18, 1.71)	1.98 (1.59, 2.62)	17.7	<**.001**
	17	1.41 (1.19, 1.75)	1.63, (1.37, 2.04)	6.0	**.020**
	20	1.42 (1.16, 1.83)	1.44 (1.21, 1.80)	<1	.849

Statistical analyses were performed on transformed data. Estimated means and endpoints of confidence intervals were back-transformed into the original measurement units. Degrees of freedom = 1/32 for all tests.